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REDDIG, PETER J				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary

Application No.

10/521,410

Applicant(s)

ULLRICH ET AL.

Examiner

PETER J. REDDIG

Art Unit

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Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01/03/2011.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-14 and 17-39 is/are pending in the application.
- 4a) Of the above claim(s) 1-9 and 22-34 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 10-14, 17-21 and 35-39 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-945)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 8/31/10 1/3/11
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

1. The Amendment filed January 3, 2011 in response to the Office Action of November 2, 2010 is acknowledged and has been entered. Claim 10 has been amended.
2. Claims 1-14 and 17-39 are pending.
3. Claims 1-9 and 22-34 have been previously withdrawn from consideration.
4. Claims 10-14, 17-21, and 35-39 are currently under consideration.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 10-14, 17-21, and 35-39 remain rejected under 35 U.S.C. 112, first paragraph, for the reasons of record set forth below.

... because the specification, while being enabling for a method of reducing the invasivity of cancer cells in a subject in need thereof comprising administering to the subject an inhibitor of the AXL protein selected from the group consisting of anti-AXL antibodies or Fab, Fab', Fab2 or scFV antigen binding fragments thereof or an inhibitor of GAS6 selected from the group consisting of anti-GAS6 antibodies or Fab, Fab', Fab2 or scFV antigen binding fragments thereof, and wherein said cancer cells are selected from the group consisting of breast cancer cells, prostate cancer cells, kidney cancer cells, glioblastoma cells or cancer cells of epithelial origin, does not reasonably provide enablement for a method of reducing the invasivity of cancer cells in a subject in need thereof comprising administering to the subject an inhibitor of the AXL gene, AXL ligand gene, AXL protein or AXL protein ligand, or any combination thereof, in an amount which is effective for reducing the invasivity of cancer cells, and wherein said inhibitor of the AXL protein is selected from the group consisting of anti-AXL antibodies or Fab, Fab', Fab2 or scFV antigen binding fragments thereof, and wherein said cancer cells are selected from the group consisting of breast cancer cells, prostate cancer cells, kidney cancer cells, glioblastoma cells or cancer cells of epithelial origin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

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The factors to be considered in determining whether undue experimentation is required are summarized in *re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). The court in *Wands* states: "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are broadly drawn to a method of reducing the invasivity of cancer cells in a subject in need thereof comprising administering to the subject an inhibitor of the AXL gene, AXL ligand gene, AXL protein or AXL protein ligand, or any combination thereof, in an amount which is effective for reducing the invasivity of cancer cells, and wherein said inhibitor of the AXL protein is selected from the group consisting of anti-AXL antibodies or Fab, Fab', Fab2 or scFv antigen binding fragments thereof, and wherein said cancer cells are selected from the group consisting of breast cancer cells, prostate cancer cells, kidney cancer cells, glioblastoma cells or cancer cells of epithelial origin.

The specification teaches that the inhibitor of the AXL gene, AXL ligand gene, AXL protein or ligand thereof, e.g. GAS6, may be an antibody, a biologically active nucleic acid or a low molecular weight compound, e.g. a peptide or a non-peptidic organic compound. See p. 6.

The specification teaches that in a preferred embodiment the inhibitor is an antibody directed against the AXL protein or a ligand thereof, e.g. GAS6. The term "antibody" relates to polyclonal antibodies and monoclonal antibodies, particularly to chimeric or humanized monoclonal antibodies or to human antibodies. Further, the term comprises antibody fragments, e.g. proteolytic fragments such as Fab, Fab' or F(ab)2 fragments or recombinant fragments such as single chain antibody fragments, e.g. scFv fragments. Methods of manufacturing antibodies or antibody fragments as described above are known in the art. See p. 6-7

The specification teaches that in a further preferred embodiment the inhibitor is a biologically active nucleic acid, e.g. a DNA, an RNA or a synthetic nucleic acid analog. Preferred examples of biologically active nucleic acids are antisense nucleic acids, ribozymes or RNA interference molecules directed against the AXL gene or an AXL ligand gene or a transcript thereof. A further preferred example of a biologically active nucleic acid is a dominant-negative mutant of the AXL gene. Biologically active nucleic acids may be delivered by known procedures, e.g. by using viral or non-viral gene transfer vectors. See p. 7.

The specification teaches that in a further preferred embodiment the inhibitor is a peptidic compound, e.g. a peptide having a length of from 4 to 25 amino acids, a cyclic peptide, a peptide, derivative or a peptide mimetic derived from such a peptide. Alternatively the low-molecular weight inhibitor may be a non-peptidic, organic compound, e.g. an inhibitor of AXL kinase activity. Low-molecular weight inhibitors may be obtained by screening suitable compound libraries in a method as described, in more detail below. See p. 7.

The specification places no limitation on the AXL protein ligands or the genes that encode them. Thus, given the above, the claims encompass using a large genus of inhibitors of the AXL gene, AXL ligand gene, and AXL protein ligand to reduce invasivity of cancer cells in a subject

The specification teaches that overexpression of the receptor tyrosine kinase AXL/UFO (Genbank accession No. M 76125) has been implicated in the development of human hematological malignancies. Further, very recent data indicate that signaling of AXL and its ligand GAS6 is involved in angiogenesis, adhesion and survival of cancer cells, see p.1, lines 15-19.

The specification teaches that the present invention relates to the diagnosis or the prevention and/or treatment of malignant disorders, particularly the tumor invasivity and/or metastasis formation in malignant disorders. Preferred examples of malignant disorders are cancers of the breast, prostate, kidney, colon, lung and glioblastomas. More preferably, the malignant disorder is breast cancer or glioblastomas, see p. 5, lines 14-19.

The specification teaches that Axl mRNA was expressed in primary breast cancer tumors, and other tumors and cancer cell lines (kidney, prostate and glioblastomas) as well, see p. 25, line 22 to p. 26, line 10 and Fig. 2-4.

The specification teaches that an antibody to the extracellular domain of Axl or dominant negative mutant of AXL (dnAXL) transduced by retrovirus can inhibit the migration and invasion of breast cancer cell lines and a prostate cancer cell line into Matrigel in a Boyden chamber in vitro assay, see p. 21-26, and figures 5-7.

The specification teaches that dnAXL transfected glioblastoma cells exhibited inhibited growth and invasion in vivo and in vitro. See p. 32-36 and Fig. 8-11.

One cannot extrapolate the teachings of the specification to the enablement of the claims because a nexus has not been established between inhibiting Axl gene, Axl ligand gene, and Axl protein ligand with the broadly contemplated and claimed inhibitors thereof because the development of therapeutics for cancer and the design and delivery of inhibitors is well known in the art to be unpredictable and without further guidance one of skill in the art would not be able to make and use the broadly claimed method without undue experimentation..

As drawn to the unpredictability of drug development for cancer, Gura (Science, 1997, 278:1041-1042, previously cited) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Furthermore, Kaiser (Science, 2006, 313: 1370, previously cited) teaches that 90% of tumor drugs fail in patients, see 3rd col., 2nd to last para. Thus, given the above, in absence of further guidance on making and using the broadly claimed inhibitors, one of skill in the art could not make and use the method used for the reducing the invasivity of cancer cells without undue experimentation.

Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65, previously cited) teaches that tumors resist penetration by drugs (p.58, col. 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col. 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39, previously cited) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular

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mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col. 2). In addition the inhibitors must accomplish several tasks to be effective. They must be delivered into the circulation that supplies the cancer and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. Also, the target cell must not have an alternate means of inducing invasion despite action at the proper site for the inhibitors. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The inhibitors may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half-life of the antibody. In addition, the inhibitors may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where it has no effect, circulation into the target area may be insufficient to carry the antibody and a large enough local concentration may not be established. Thus, given the breadth of the claimed inhibitors, in the absence of sufficient guidance for making and using these inhibitors for reducing the invasivity of cancer cells, and given the unpredictability in the art, one of skill in the art would not be able to make and use the method as broadly claimed without undue experimentation.

Additionally, as drawn to nucleic acid inhibitors of the Axl gene or Axl ligand gene the art teaches that are problems with these technologies making their use unpredictable without sufficient guidance and direction. For example, Gura (Science, 1995, 270:575-577) teaches that researchers have many concerns with the antisense therapy. Gura discloses that "the biggest concern is that antisense compounds simply don't work the way researchers once thought they did." Other drawbacks in animal studies include difficulty getting antisense oligonucleotides to target tissues and the existence of potentially toxic side effects such as increased blood clotting and cardiovascular problems (page 575, col. 1, para 2). Another problem stems from the fact that oligonucleotides used as controls produced the same biological effects in cell culture as did the antisense compounds (page 576, col. 1, para. 2 and 3). In addition, Gura reports problems with synthetic antisense oligonucleotides in that unwanted and sometimes lethal side effects occurred in animal experiments, and that they block cell migration and adhesion to underlying tissue *in vitro* (page 576, col.3, para.1 and 3). Thus a high degree of unpredictability is associated with the use of antisense constructs employed in methods of inhibiting expression of a particular gene *in vivo*. Additionally, Scherer and Rossi (Nature Biotechnology 2003, 21: 1457-1465) teach that the challenges that need to be met for therapeutic use of anti-sense technologies like antisense oligonucleotides, RNA interference, and ribozymes include obtaining efficient delivery, enhancing stability, minimizing off target effects and identification of sensitive sites in the RNA target. See Abstract. Scherer and Rossi teach that finding an effective target site in mRNA for these anti-sense technologies can be problematic, with the major limitation being identification of sequence/antisense combination that provides potent knockdown of the target RNA at a low concentration of antisense agent. See ¶ bridging p. 1461-1462. Scherer and Rossi teach that off target effects of these anti-sense technologies is another problem, which could lead to unwanted side effects when using anti-sense technologies. See 1462-1463. Additionally, Scherer and Rossi teach that efficient delivery is the limiting factor for

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use of the antisense compounds and, as of publication of the article; there was no single reagent or modification that can be effectively used for all the different antisense agents. See p. 1463-1st col. Thus, in absence of sufficient guidance and/or exemplification for targeting the Axl gene or Axl ligand gene with the broadly completed inhibitors, including nucleic based inhibitors, undue experimentation would be required to make and use the method as broadly claimed.

Furthermore, the use of the antisense technologies and the dominant negative mutant of the Axl gene encompass using vectors and delivery methods that fall under gene therapy technologies. Gene therapy using administration of recombinant nucleic acids involving in vivo or ex vivo methods had seen little success at the time the invention was made despite a great deal of work and resources. Several reviews in the art show that difficulties with vector selection, mode of delivery and persistence of predictable and effective levels of expression of the protein, created technical barriers to the practice of gene therapy methods. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery...", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" Verma et al. ((1997) *Nature* Volume 389, page 239, column 3, and paragraph 2). Marshall concurs, stating that, "difficulties in getting genes transferred efficiently to target cells- and getting them expressed-remain a nagging problem for the entire field", and that "many problems must be solved before gene therapy will be useful for more than the rare application" Marshall ((1995) *Science*, Volume 269, page 1054, column 3, paragraph 2, and page 1055, column 1).

Numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck et al. (Goodman & Gilman's The Pharmacological Basis of Therapeutics (1996), 9th Edition, Chapter 5, McGraw-W, NY) explains, "the delivery of exogenous DNA and its processing by target cells requires the introduction of new pharmacokinetic paradigms beyond those that describe the conventional medicines in use today". Eck et al. teaches that with in vivo gene transfer, one must account for the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the in vivo consequences of altered gene expression and protein function, the fraction taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell or its secretory fat, once produced. These factors differ dramatically based on the vector used, the protein being produced and the disease being treated (see Eck et al. bridging pages 81-82).

Also among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are, immune responses and the identity of the promoter used to drive gene expression. Verma et al. teaches, in reference to ex vivo methods, that weak promoters produce only low levels of therapeutically effective protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein be achieved (Verma et al., supra, page 240, column 2). Verma et al. further warns that, "... the search for such combinations is a case of trial error for a given cell type" (Verma et al., supra, page 240, bridging sentence of columns 2-3). The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross et al. *Human Gene Therapy*, 1996, Volume 7, pages 1781-1790, see page 1789, column 1, first paragraph). Thus, the art at the time of filing clearly establishes that expectation for achieving a desired

therapeutic effect in vivo by expressing a therapeutic gene using any of the expression constructs known in the art was extremely low.

More recently, Rubanyi (Mol. Aspects Med. (2001) 22:113-142) teaches that the problems described above remain unresolved. Rubanyi states, "[although theoretical advantages of human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far..." See page 113, paragraph 1. Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene delivery vectors and improvement in gene expression control systems (see section 3. "Technical hurdles to be overcome in the future", beginning on page 116 and continued through page 125). Furthermore, Juengst (British Medical Journal (2003) Volume 326, pages 1410-1411) teaches the unpredictable nature of gene therapy and that a few of the apparent successes actually developed T cell-acute lymphoblastic leukemia due to insertional mutagenesis at or near the LMO-2 gene causing altered gene expression. The art has demonstrated that a large amount of experimentation has already been performed without demonstrating successful gene therapy methods for treatment of disease.

Thus, in order to practice the claimed invention, the skilled artisan would not have found sufficient guidance in the specification to achieve effective levels of the expressed nucleic acid, to select a proper dose or administration route or to determine other factors for a successful treatment. The prior art did not compensate for the lack of guidance in the specification since the teachings do not recognize any clearly successful gene therapy methods. The skilled artisan would have had to engage in a large amount of experimentation to practice the claimed invention. In view of the lack of guidance and the large amount of experimentation in an unpredictable art, it would require undue experimentation to practice the claimed invention.

Given the above, in the absence sufficient guidance and direction demonstrating reduction of invasivity of cancers with the broadly claimed inhibitors to the Axl gene, Axl ligand gene and Axl ligand protein, one of skill in the art could not predictably practice the claimed invention without undue experimentation.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides insufficient working examples which would provide guidance to one skilled in the art and insufficient evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated or claimed with a reasonable expectation of success.

For the above reasons, undue experimentation would be required to practice the claimed invention.

Applicants argue that the Examiner has rejected claims 10-14, 17-21 and 35-39 under 35 USC § 112, first paragraph for lacking enablement. As to independent claim 10, the Examiner has essentially reiterated his reasoning for the rejection from the prior Office Action, and applied the same reasoning to new claims 37-39.

Applicants argue that however, Applicants note that the Examiner concedes the specification does enable a method for reducing the invasivity of prostate cancer cells by administering an anti-AXL antibody (Office Action, para. spanning pp. 2-3). This is essentially the embodiment to which claim 39 is directed. Thus, the Examiner's rejection of claim 39 seems to be an error, and Applicants request that it be withdrawn.

Applicants argue that regarding the remaining claim rejections, Applicants note that the Examiner rejects the embodiments regarding the inhibition of AXL gene expression, and administration of an inhibitor of the AXL gene or of an inhibitor of the AXL ligand gene. Applicants disagree with the Examiner's interpretation of the claims. However, solely in the interest of expediting prosecution, Applicants have amended claims 10 and 38, as discussed above. As a result of these amendments, the rejected embodiments have been removed from the claims. Accordingly, this rejection has been obviated and should be withdrawn.

Applicants' arguments have been considered, but have not been found persuasive because the claims still encompass and claim non-enabled embodiments. In particular, claim 10 and its dependent claims are still drawn to inhibitors of AXL protein ligand. Additionally claims 13, 20, 21, and 37 still recite or are drawn to inhibitors of the AXL gene. Furthermore, claim 38 now

recites an inhibitor of the interaction between the AXL protein and GAS6. Thus, the amended claims still encompass embodiments found not to be enabled. With regard to claim 39, although it limits the inhibitor of the Axl protein to an anti-AXL antibody, it does not exclude the inhibitor of an AXL protein ligand of the base claim or other non-enabled embodiments encompassed by the base claim. Thus, the rejection is maintained for the reasons of record.

6 Claims 10-14, 17-20, and 35-38 are rejected as failing to comply with the written description requirement for the reasons of record set forth below.

The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to a method of reducing the invasivity of cancer cells in a subject in need thereof comprising administering to the subject an inhibitor of the AXL gene, AXL ligand gene, AXL protein or AXL protein ligand, or any combination thereof, in an amount which is effective for reducing the invasivity of cancer cells, and wherein said inhibitor of the AXL protein is selected from the group consisting of anti-AXL antibodies or Fab, Fab', Fab2 or scFv antigen binding fragments thereof, and wherein said cancer cells are selected from the group consisting of breast cancer cells, prostate cancer cells, kidney cancer cells, glioblastoma cells or cancer cells of epithelial origin.

The specification teaches that the inhibitor of the AXL gene, AXL ligand gene, AXL protein or ligand thereof, e.g. GAS6, may be an antibody, a biologically active nucleic acid or a low molecular weight compound, e.g. a peptide or a non-peptidic organic compound. See p. 6.

The specification teaches that in a preferred embodiment the inhibitor is an antibody directed against the AXL protein or a ligand thereof, e.g. GAS6. The term "antibody" relates to polyclonal antibodies and monoclonal antibodies, particularly to chimeric or humanized monoclonal antibodies or to human antibodies. Further, the term comprises antibody fragments, e.g. proteolytic fragments such as Fab, Fab' or F(ab)2 fragments or recombinant fragments such as single chain antibody fragments, e.g. scFv fragments. Methods of manufacturing antibodies or antibody fragments as described above are known in the art. See p. 6-7

The specification teaches that in a further preferred embodiment the inhibitor is a biologically active nucleic acid, e.g. a DNA, an RNA or a synthetic nucleic acid analog. Preferred examples of biologically active nucleic acids are antisense nucleic acids, ribozymes or RNA interference molecules directed against the AXL gene or an AXL ligand gene or a transcript thereof. A further preferred example of a biologically active nucleic acid is a dominant-negative mutant of the AXL gene. Biologically active nucleic acids may be delivered by known procedures, e.g. by using viral or non-viral gene transfer vectors. See p. 7.

The specification teaches that in a further preferred embodiment the inhibitor is a peptidic

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compound, e.g. a peptide having a length of from 4 to 25 amino acids, a cyclic peptide, a peptide, derivative or a peptide mimetic derived from such a peptide. Alternatively the low-molecular weight inhibitor may be a non-peptidic, organic compound, e.g. an inhibitor of AXL kinase activity. Low-molecular weight inhibitors may be obtained by screening suitable compound libraries in a method as described, in more detail below. See p. 7.

The specification places no limitation on the AXL protein ligands or the genes that encode them. Thus, given the above, the claims encompass using a large genus of inhibitors of the AXL gene, AXL ligand gene, and AXL protein ligand to reduce invasivity of cancer cells in a subject and a large genus of AXL ligands and AXL ligand genes. The genus of inhibitors and genus of AXL ligands and AXL ligand genes are highly diverse, with the members varying significantly both in structure and function. The description of a polyclonal antibody directed to the extracellular portion of AXL that inhibits the migration of cell lines in vitro (see p. 26-lines 24-28 and Fig. 6) and the dominant negative mutant of Axl (See p. 32-36 and Fig. 8-11) fails to adequately describe the genus of inhibitors because said genus tolerates members which differ significantly in both structure and function from said antibody to AXL protein or the dnAXL. Additionally, the description of GAS6 does not provide adequate support for the genus of AXL protein ligands and AXL ligand genes. One of skill in the art can reasonably conclude that applicant was not in possession of the genus inhibitors of the AXL gene, AXL ligand gene, and AXL protein ligand and the genus of AXL protein ligands or AXL ligand genes at the time the invention was filed. Because the genus of inhibitors of the AXL gene, AXL ligand gene, and AXL protein ligand and the genus of AXL protein ligand and AXL ligand gene are not adequately described, the method claims relating to said genera are also not adequately described.

As it is drawn to the DNA arts, the findings in *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Id.* At 1567, 43 USPQ2d at 1405. The court also stated that a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. *Id.* At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." *Id.*

It is noted that as of the filing date antibodies that inhibit AXL protein activity and GAS6 were known in the art (see U.S. Pat. No. 5,468,634 col. 7, line 60 to col. 8 line 30, previously

cited, and USPN 5,538,861), however, this fail to adequately describe an entire genus because the genus is highly variant encompassing members which differ significantly in structure from the few art known inhibitors or GAS6.

In the instant case the genus is only described as a definition by function (i.e. inhibition of AXL gene, AXL ligand protein or gene or binding of AXL), and beyond the example of antibodies and dnAxl or GAS6, one of skill in the art cannot readily visualize or recognize the identity of members of the genus or know what that material consists of.

Additionally, the following teaching of the Federal Circuit as set out in *Noelle v. Lederman*, 69 USPQ2d 1508 (Fed. Cir. 2004) 355 F3d 1343 clearly applies to the instant claimed invention as drawn to antibodies or fragments to the broadly the broadly claimed Axl protein ligand. The court teaches as follows: "Noelle did not provide sufficient support for the claims to the human CD40CR antibody in his '480 application because Noelle failed to disclose the structural elements of human CD40CR antibody or antigen in his earlier '799 application. Noelle argues that because antibodies are defined by their binding affinity to antigens, not their physical structure, he sufficiently described human CD40CR antibody by stating that it binds to human CD40CR antigen. Noelle cites *Enzo Biochem II* for this proposition. This argument fails, however, because Noelle did not sufficiently describe the human CD40CR antigen at the time of the filing of the '799 patent application. In fact, Noelle only described the mouse antigen when he claimed the mouse, human, and genus forms of CD40CR antibodies by citing to the ATCC number of the hybridoma secreting the mouse CD40CR antibody. If Noelle had sufficiently described the human form of CD40CR antigen, he could have claimed its antibody by simply stating its binding affinity for the "fully characterized" antigen. Noelle did not describe human CD40CR antigen. Therefore, Noelle attempted to define an unknown by its binding affinity to another unknown. As a result, Noelle's claims to human forms of CD40CR antibody found in his '480 application cannot gain the benefit of the earlier filing date of his '799 patent application. Moreover, Noelle cannot claim the genus form of CD40CR antibody by simply describing mouse CD40CR antigen". *Noelle v. Lederman*, 69 USPQ2d 1508 (Fed. Cir. 2004) 355 F3d 1343 at 1514.

Thus to satisfy the written description requirement for the broadly claimed genus of the Axl ligand proteins bound by the antibodies must be adequately described. The Federal Circuit further addresses this issue in *In re Alonso*, 88 USPQ2d 1849 (Fed. Cir. 2008) 545 F3d 1015, "The specification of the '749 Application does not characterize the antigens to which the monoclonal antibodies must bind; it discloses only the molecular weight of the one antigen identified in Example 2. This is clearly insufficient. The specification teaches nothing about the structure, epitope characterization, binding affinity, specificity, or pharmacological properties common to the large family of antibodies implicated by the method. While Alonso's claim is written as a method, the antibodies themselves are described in purely structural language — "a monoclonal antibody idiotype to the neurofibrosarcoma of said human." This sparse description of antibody structure in the claim stands in stark contrast to the detailed method of making the antibodies found in the specification" *In re Alonso*, 88 USPQ2d 1849 (Fed. Cir. 2008) at 1853.

The instant specification has only described GAS6, thus it fails to describe the genus of antibodies to the AXL protein ligand. Therefore, since the claims encompass a genus based on unknown AXL protein ligands, it is unclear what structures would identify members of the genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the ‘written description’ inquiry, whatever is now claimed.” (See page 1117.) The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See Vas-Cath at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genera, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolation. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

Thus, given the above, the specification does not provide an adequate written description of the genus of inhibitors of the AXL gene, AXL ligand gene, and AXL protein ligand and the genus of AXL protein ligand and AXL ligand gene

Applicants argue that the Examiner has rejected claims 10-14, 17-20 and 35-38 under 35 USC § 112, first paragraph, for failing to comply with the written description requirement. The Examiner argues that the claims are drawn to an “inhibitor of the AXL protein” which encompasses a huge genus of compounds with different structures and functions, and the specification does not adequately describe this genus of agents, and that it specifically does not provide the structure or the structure-function correlation of these inhibitors.

Applicants argue that they disagree with the Examiner's interpretation of the claims. However, as discussed above, Applicants have amended the claims solely to expedite prosecution. With these amendments, the limitation regarding the AXL protein ligand has been more clearly articulated, and the written description support for this limitation has been clearly defined. As such, this rejection has been obviated and should be withdrawn.

Applicants’ arguments have been considered, but have not been found persuasive because the claims still encompass a large genus of inhibitors that do not have adequate written description. In particular, claim 10 and its dependent claims are still drawn to inhibitors of AXL

protein ligand. Additionally claims 13, 20, 21, and 37 still recite or are drawn to inhibitors of the AXL gene. Furthermore, claim 38 now recites an inhibitor of the interaction between the AXL protein and GAS6. Thus, the amended claims still encompass embodiments found not to be not to have an adequate written description. Thus, the rejection is maintained for the reasons of record.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7 Claim 10-14, 18-20, and 35-39 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 01/30964 A2 (Burmer et al. 3 May 2001) for the reasons of record set forth below

WO 01/30964 teaches using anti-sense and ribozyme oligonucleotides to the AXL gene and antibodies to the AXL protein (including F(ab)₂, Fab', Fab, and sc FV fragments) to treat cancer and reduce metastasis of the liver, kidney, breast, colon or prostate in humans and reduce the expression of Axl. See Claims 10-12, Table 1-p.66, p. 4-lines 4-25, p. 5-8, p. 12-lines 13-15, p. 30-lines 1-5 and p. 35-39.

Although the reference does not specifically state that the method is a method of reducing the invasivity of cancer cells or inhibiting AXL protein activity or interaction with its ligand, given that prostate and kidney cancer patients are a subject in need of reduced invasivity of cancer cells and an inhibitor of the AXL gene/protein is being administered to that population, the claimed method appears to be the same as the prior art method, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the method of the prior art does not possess the same material, structural and functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed method is different from those taught by the prior art and to establish patentable differences. See *In re Best* 562F.2d 1252, 195 USPQ 430 (CCPA 1977).

Applicants argue that Burmer is directed to isolated nucleic acids and proteins associated with cancer. The Examiner argues that these references disclose all of the claim limitations except the method of reducing the invasivity of cancer cells. However, the Examiner essentially argues that reducing invasivity would be an inherent property of each of the disclosed methods, and, therefore, these references anticipate the rejected claims.

Applicants argue that for a prior art reference to inherently disclose a claim limitation, that limitation must necessarily flow from practicing the claimed method. However, practicing the method of Burmer, would necessarily result in the reduction of invasivity of cancer cells. Therefore, this references does not inherently disclose the claim limitation regarding reducing the invasivity of cancer cells. In addition, independent claim 10 is directed to a method of reducing the invasivity of cancer cells in a subject in need of such treatment. Applicants argue that Burmer is also silent as to this aspect of claim 10. Applicants argue that further, practicing the method of Burmer would not necessarily result in reducing the invasivity of cancer cells in a subject in need of such treatment. Applicants argue that as such, Burmer does not inherently disclose the "in need thereof" limitation of independent claim 10.

Applicants' arguments have been considered, but have not been found persuasive. The term reducing invasivity of cancer cells in the subject is not limited by the specification and thus reads on treating metastatic cancer cells which are invasive as they invade other tissues when they are metastatic. Thus given that Burmer teaches treating cancer and reducing metastasis with antibodies to the AXL protein (including F(ab)₂, Fab', Fab, and sc FV fragments), the claims are anticipated and the rejection is maintained for the reasons previously set forth.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. Claims 10-12, 14, 18, 19, 35, 36, 38 and 39 remain rejected under 35 U.S.C.

103(a) as being unpatentable over USPN 5,468,634 (Liu E. T. 1995, previously cited) in view of WO 89/06692 (Hudziak et al. 1989), in further view of USPN 5,538,861 (Schneider et al. 1996) and in further view of Jacob et al. (Cancer Detection and Prevention 1999, 23:325-332) for the reasons of record, set forth below.

USPN 5,468,634 teaches using an antibody that inhibits Axl receptor function for therapeutic purposes in methods described by WO 89/06692. USPN 5,468,634 teaches that inhibition can be achieved with an antibody blocks receptor function or stimulates receptor function through down regulation. USPN 5,468,634 teaches using antibodies to the extracellular domain conjugated to ricin A chain for therapeutic purposes. See ¶ bridging col. 7 and 8. USPN 5,468,634 teaches that F(ab)₂, Fab', and Fab fragments of the anti-Axl antibody. See. col. 7-lines 30-60. USPN 5,468,634 teaches that Axl was seen in most human cell lines tested, including breast cancer cell lines. See Col. 16 and Table 1.

USPN 5,468,634 does not specifically teach reducing the invasivity of cancers in subject with cancers cells of the breast, prostate, kidney, glioblastoma, or cancer cells of epithelial origin.

WO 89/06692 teaches treating inhibiting the growth and metastasis of tumor cells, including breast cancer, with antibodies that inhibit growth factor receptor function, antibodies that inhibit the function of the receptor ligand, and antibodies to the receptor conjugated to cytotoxic moieties. See abstract, p. 8-line 20 to p. 10-line 20, p. 15-lines 15-35, p.21-22 and claims 16-36.

USPN 5,538,861 teaches anti-GAS6 antibodies that can be used to block GAS6 activation of Axl and cell growth. See col. 14-lines 25-60 and Fig. 10.

Jacob et al. teach that Axl is overexpressed in prostate carcinoma cell lines compared to normal prostate cells. See Abstract and Figure 2. Jacob et al. teach that the overexpression of Axl indicates a linkage between Axl expression and tumorigenesis and metastasis of the prostate. See p. 329-1st ¶.

It would have been *prima facie* obvious at the time the invention was made to combine the teachings of USPN 5,538,861, WO 89/06692, and USPN 5,538,861 and use the antagonistic or cytotoxin labeled antibody to AXL of USPN 5,468,634 or the antagonistic GAS-6 antibody of USPN 5,538,861 to treat breast cancer with the methods WO 89/06692 because USPN 5,538,861 specifically points the methods WO 89/06692 for use of the therapeutic AXL antibodies and USPN 5,538,861 teaches that Axl is expressed in breast cancer. Additionally, given that WO 89/06692 teaches using antibodies to inhibit the growth factor receptor ligand for treatment of breast cancer and metastasis, it would have been obvious use the anti-GAS6 antibodies of USPN 5,538,861 for treatment. Furthermore, given that Jacob et al. teach the overexpression of AXL in prostate carcinoma cells and AXL's importance in tumorigenesis and metastasis of the prostate, it would have been obvious to perform the method on subjects with prostate cancer cells. Given the importance of developing new cancer therapeutics and given that the antagonistic AXL and Gas6 antibodies were taught in the art, one of skill in the art would have been motivated with a reasonable expectation of success of making and using the antibodies for treatment of cancer.

Although the references does not specifically state that the method is a method of reducing the invasivity of cancer cells, given that breast and prostate cancer patients are subjects in need of reduced invasivity of cancer cells and an inhibitor of the AXL protein/ligand is being administered to that population, the claimed method appears to be the same as the combined methods of the prior art, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the method of the prior art does not possess the same material, structural and functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed method is different from those taught by the prior art and to establish patentable differences. See *In re Best* 562F.2d 1252, 195 USPQ 430 (CCPA 1977).

Applicants argue that the Examiner argues that each reference discloses various claim limitations, and that one of skill in the art would have known to combine the references to arrive at the presently claimed subject matter, thus rendering these claims obvious. However, as with the anticipation rejections discussed above, the Examiner concedes that none of the cited references discloses the reducing invasivity limitation and again relies on inherent disclosure in making the rejection.

Applicants argue that as with the references cited in conjunction with the anticipation rejection, practicing the methods cited here would not necessarily result in the reduction of invasivity of cancer cells. Therefore, these references do not inherently disclose the claim

imitation regarding reducing the invasivity of cancer cells, and, consequently, the disclosures in these references, whether considered alone or in combination, cannot render obvious the present claims.

Applicants' arguments have been considered, but have not been found persuasive. The term reducing invasivity of cancer cells in the subject is not limited by the specification and thus reads on treating metastatic cancer cells which are invasive as they invade other tissues when they are metastatic. Thus given that treating metastatic cancers would be obvious in view of the cited art the claims are obvious and the rejection is maintained for the reasons previously set forth.

9. All other objections and rejections recited in Office Action of May 6, 2010 are withdrawn.

10. No claims allowed.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Misook Yu can be reached on (571) 272-0839. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Peter J Reddig/
Primary Examiner, Art Unit 1642